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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,092	05/18/1999	MICHAEL PAULISTA	P564-9010	9258

6449 7590 10/01/2003

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	30

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,092	PAULISTA ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-25,28,30,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-25,28,30,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response filed on 03/24/03 and 7/22/03 has been acknowledged.

Claims 17-25, 28, 30 and 32-33 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim, ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 112

Claims 17-25, 28, 30 and 32-33 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons of record as set forth in the office action mailed on 10/23/02.

Nature of Invention:

Invention relates to a method of treatment of bone defects and an implant material suitable for cartilage, bone or cartilage and bone growth comprising crystallographically phase-pure calcium phosphate and fragments of MP52 protein (as claimed).

Breadth of Claims and Guidance Provided in the Specification:

The instant claims are drawn to an implant for cartilage and/or bone growth comprising a crystallographically phase-pure calcium phosphate matrix and a cartilage and/or bone inducing MP52 protein or DNA encoding the MP52 protein, wherein the MP52 protein is selected from the group consisting of fragments of SEQ ID No:1, which is a homodimer (as claimed) and a dimer of another protein of TGF-beta super-family.

The instant claims are further drawn to a method of treating a disease, which affect cartilage and/or bone and/or damage to cartilage and/or bone in a patient by implanting the implant material as claimed.

The specification states that many members of TGF-beta, BMP and GDF subfamilies have cartilage and/or bone inducing potentials. The specification further states that it can be assumed that a combination of various factors would be advantageous for the efficiency of cartilage and bone induction (spec. page 3, para.1). The specification further teaches the use of crystallographically phase-pure alpha and beta tricalcium phosphate ceramics in making of the implant as claimed (spec. 13, para.1). In addition the specification suggested that the efficacy of the implant material could be tested in conventional test systems such as animal models (spec. page 19-20). However, the instant specification fails to disclose that the implantation of the implant material (as claimed) leads to bone or cartilage formation in any and all animals. The specification even fails to provide a single working example that a protein encoded by SEQ ID NO:1 or its fragments (as claimed) have any bone and/or cartilage inducing potential in any and all animals.

State of Art and Predictability

The state of the art at the time of filing teaches that the signal transduction mechanism of members of TGF-beta superfamily is complex and the members are know to regulate plethora of developmental processes (Attisano et al, Science. 296:1646-1647, 20002). For example, proteins of the TGF-beta superfamily bind to two different types of signaling receptors termed as type II and type I receptors. Upon ligand binding and formation of type II and type I receptor complexes, followed by possible receptor conformational changes, type I receptors are phosphorylated and activated by type II receptor kinases. Type I receptor kinases then transmit intracellular signals by phosphorylating Smad proteins. In mammals, only five type II receptors and seven type I receptors have been identified. It is theoretically possible to form more than 30 different combinations of type II and type I receptors. However, certain type II receptors tend to interact with certain type I receptors. Thus, the combinations of type II and type I receptors appear to be limited under physiological conditions and the variety of ligands converge at the receptor level (Miyazono et al, J Cell Physiol, 187(3):265-76, 2001). The instant specification fails to disclose that MP52

modulates bone and/or cartilage formation via TGF-beta signal transduction pathway. In addition, the specification fails to disclose what are another dimmer of TGF-beta superfamily that in combination with MP52 that would leads to cartilage and/or bone formation.

Furthermore, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited fragment of SEQ ID NO:1 are mere hypothetical fragments since the specification fails to disclose that these fragments possess any bone or cartilage formation activity. In addition, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Thus, in order to elucidate the roles of TGF-beta and a morphogenetic protein in clinical disorders it is very important to understand the signaling mechanisms of those proteins in vivo (see Miyazono, page 272, conclusion).

Response to arguments

The applicant argues that since MP52 is a member of TGF-β family active fragments of MP52 are predictable. The applicant argues that Poehling, Spiro and Nishitoh show MP52 uses type I and II receptors i.e. it follows the same signaling mechanism as other TGF-b family members. The applicant argues that on page 3 the instant specification states that many members of TBF-β super family show a cartilage and/or bone inducing potential. Therefore in view of such disclosure one skill in the art could easily determine which of the proteins of the TGF-b superfamily can be used in combination with MP52 (response filed 07/07/03 pages 3-6). In addition the applicant provided Gerturd Hottens's declaration, which demonstrates a C-terminal part of MP52 (119 amino acids) containing amino acids 383-501 of SEQ ID NO:1 is useful for the treatment of bone damage or cartilage damage (declaration under 37 CFR 1.132).

However, this is found NOT persuasive because Poehling, Spiro and Nishitoh only teaches the use of full length GDF-5/MP52 protein and fails to disclose that MP52 fragments (as claimed) have any bone or cartilage forming activity. At best Gerturd Hottens's declaration only teaches that C-terminal part of MP52 (119 amino acids) containing amino acids 383-501 of SEQ ID NO:1 is useful for the treatment of bone damage or cartilage damage. The declaration fails to disclose that any other fragments of SEQ ID NO:1, which is a homodimer and a dimer of another protein of TGF-beta super-family (as claimed) have any bone and/or cartilage inducing potential in an animal. The earlier office action clearly provided the evidence that the signal transduction mechanism of members of TGF-beta superfamily is complex and the members are know to regulate plethora of developmental processes (see Attisano et al, Science. 296:1646-1647, 20002). In mammals, only five type II receptors and seven type I receptors have been identified. It is theoretically possible to form more than 30 different combinations of type II and type I receptors. However, certain type II receptors tend to interact with certain type I receptors. Thus, the combinations of type II and type I receptors appear to be limited under physiological conditions and the variety of ligands converge at the receptor level (Miyazono et al, J Cell Physiol, 187(3):265-76, 2001). The instant specification fails to disclose that MP52 fragments (as claimed) in combination with a dimmer of another protein of the TGF-b superfamily show any cartilage or bone inducing activity.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case use of any fragment of MP52 protein (as claimed) for the treatment of any bone or cartilage defect is not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the

art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Thus, in view of lack of specific guidance in the specification, the skilled artisan at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making an implant as claimed, containing fragments of MP52 protein (as claimed) in combination with any and all dimmer of TGF-beta superfamily and testing the implant for bone and/or cartilage inducing activity in vivo for the treatment of any bone defect, bone fracture, modification of jaw region (as claimed) and periodontosis.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER